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THE THEORY OF THE GENE.

PROFESSOR T. H. MORGAN

COLUMBIA UNIVERSITY

IT is unfortunate that the method of analysis of the problems of Mendelian heredity that has been adopted in one form or another by those who work in this field, has aroused a certain amount of antagonism on the part of those whose work lies in other directions.

In the following pages I shall attempt to explain what the genetic factor means to those who use it, and then try to answer certain specific criticisms of this form of hypothesis, in a hope that a mutual understanding will remove many of the objections that have been made to this method of handling genetic problems.

The objections have taken various forms. It has been said, for instance, that the factorial interpretation is not physiological but only "static," whereas all really scientific explanations are "dynamic." It has been said that since the hypothesis does not deal with known chemical substances, it has no future before it, that it is merely a kind of symbolism. It has been said that it is not a real scientific hypothesis for it merely restates its facts as factors, and then by juggling with numbers pretends that it has explained something. It has been said that the organism is a Whole and that to treat it as made up of little pieces is to miss the entire problem of "Organization." It has been seriously argued that Mendelian phenomena are "unnatural," and that they have nothing to do with

the normal process of heredity in evolution as exhibited by the bones of defunct mammals.[1] It has been said that the hypothesis rests on discontinuous variation of characters, which does not exist. It is objected that the hypothesis assumes that genetic factors are fixed and stable in the same sense that atoms are stable, and that even a slight familiarity with living things shows that no such hard and fast lines exist in the organic world. These and other things have been said about the attempts that the students of Mendel's law have made to work out their problems.

I think, however, that while a few of these charges may appear to be serious, some of them rest on a misunderstanding of what numerical treatment of any problem in science means, and others are due to differences of definition. But the most common misunderstanding arises, I venture to think, from a confusion of the problem concerned with the sorting out of the hereditary materials (the genes) to the eggs and sperms, with the problems concerning the subsequent action of these genes in the development of the embryo.

What genes stand for can be most easily shown by means of a few familiar illustrations. Mendel's cross with yellow and green peas (or any similar case in which two characters are contrasted with each other as a pair) will serve as an example. In the second generation from such a cross the numerical results, viz., three yellow to one green, find their explanation on the assumption that the two original germ plasms (briefly the yellow and the green) or some element or elements in them separate cleanly in the germ cells of the hybrid of the first generation. This cross does not tell us whether the two germ plasms separate as wholes—one from the other—or whether only some part or parts behave in this way.

But the situation changes when two or more pairs of contrasted characters are involved in the same cross.

[1] This objection is not further considered here since it has been dealt with elsewhere ("A Critique of the Theory of Evolution," 1916, p. 84).

For example, when peas that are both yellow and round are crossed to peas that are both green and wrinkled, there appear in the second (F_2) generation not only the original combinations, yellow round and green wrinkled, but also the recombinations yellow wrinkled and green round. Here also the numerical results, 9:3:3:1, can be explained by two assumptions, viz., that, as before, each pair of characters (or their representatives) are separated in the germ cells of the hybrid (F_1) and that each pair "assorts" independently of the other pair. Obviously, here, it can no longer be the wholes of the original germ plasms that separate, for the two pairs of characters behave independently of each other; but there must be separate pairs of elements in the germ plasm that assort independently of one another.

As a matter of fact it has been found that the many pairs of characters that follow Mendel's law are independent of each other in inheritance. The only restriction that this statement calls for is in the case of linked pairs of characters of which I shall speak later.

The germ plasm must, therefore, be made up of independent elements of some kind. It is these elements that we call genetic factors or more briefly genes.

This evidence teaches us nothing further about the nature of the postulated genes, or of their location in the germ plasm. However, even if we postulated nothing more about them than their independence of each other and their distribution in the germ cells, we could still handle the Mendelian results on a purely mathematical basis that would enable us to predict what new combinations should give. This possibility alone would entirely justify the hypothesis as a scientific procedure, whatever carping critics may say to the contrary. In fact Mendel himself did not carry his analysis beyond this point, for he assumed only that definite paired elements that stand in some way for the characters of the finished plant exist in the germ plasm, and that the pairs assort independently

of each other at the time when the members of each pair separate (segregate).

But between the year 1866, when Mendel published his paper, and the present year, 1917—an interval of fifty-one years—much water has run under the Mendelian mill. In consequence we can now add certain further attributes to the rather formal characterization of the gene as deducible from Mendel's law alone. But before I discuss the evidence for these postulated attributes, I must pause for a moment to call attention to a movement that was in certain important respects a forerunner of our present standpoint.

I refer to the views of Roux and of Weismann, both of whom assumed that the germ plasm is made up of particles or determiners, as Bonnet, Spencer, Darwin and others had done before them. Their argument was largely speculative, and not of the same kind as the more recent evidence derived from Mendelian analysis. Moreover in all of Weismann's earlier and best known writings his idea of the units in heredity was more involved than are our present ideas. He thought that whole germ plasms were the units that segregated, germ plasms that differed in one or many determiners, whereas the factorial view that we follow since Mendelism came to the front assumes that the units that segregate are themselves only parts of a whole which is the sum total of all the units. In his latest book, however, Weismann accepted the evidence from Mendelism and modified his ideas accordingly.

We owe to Weismann the popularization of the view that the hereditary material is carried by the chromatin, but especially we owe to Weismann the development of the idea that the sorting out of the hereditary materials takes place at the time of the maturation process in the egg and sperm.

On the other hand, it must be emphatically pointed out that the earlier idea of Roux, adopted by Weismann, that one of the hereditary complexes is sorted out during the

cleavage process of the egg, is no longer acceptable; for there is direct evidence to show that the whole hereditary complex goes to every cell in the body. This conclusion has the most far-reaching consequences for our present views as to how factors produce their effects in the developing organism, for it follows that the machinery that separates the inherited material into its component elements is not the same mechano-chemical process that brings about differentiation in the embryo.

Gene and Character

So far I have spoken of the genetic factor as a unit in the germ plasm whose presence there is inferred from the character itself. Why, it may be asked, is it not simpler to deal with the characters themselves, as in fact Mendel did, rather than introduce an imaginary entity, the gene.

There are several reasons why we need the conception of gene. Let me illustrate by examples:—

1. *The Manifold Effects of Each Gene*

If we take almost any *mutant* race, such as white eyes in *Drosophila,* we find that the white eye is only one of the characteristics that such a mutant race shows. In the present case the solubility of the yellow pigment of the body is also affected; the productivity of the individual also; and the viability is lower than in the wild fly. All of these peculiarities are found whenever the white eye emerges from a cross, and are not separable from the white eye condition. It follows that whatever it is in the germ plasm that produces white eyes, it also produces these other modifications as well, and modifies not only such "superficial" things as color, but also such "fundamental" things as productivity and viability. Many examples of this manifold effect are known to students of heredity.

It is perhaps not going too far to say that any change in the germ plasm may produce many kinds of effects on

the body. Clearly then the character that we choose to follow in any case is only the most conspicuous or (for us) the most convenient modification that is produced. Since, however, these effects always go together and can be explained by the assumption of a single unit difference in the germ plasm, this particular element or gene in the germ plasm is more significant than the character chosen as an index for one only of the effects.

2. *The Variability of the Character is not due to the Corresponding Variability of the Gene*

All characters are variable, but there is at present abundant evidence to show that much of this variability is due to the external conditions that the embryo encounters during its development. Such differences as these are not transmitted in kind—they remain only so long as the environment that produces them remains. By inference the gene itself is stable, although the character varies; yet this point is very difficult to establish. The evidence is becoming stronger nevertheless that the germ plasm is relatively constant, while the character is variable. I shall consider this evidence in another connection. Here I wish merely to register some of the reasons why the idea of the gene is useful.

3. *Characters that are Indistinguishable may be the Product of Different Genes*

We find, in experience, that we can not safely infer from the appearance of the character what gene is producing it. There are at least three white races of fowls produced by different genes. We can synthesize white-eyed flies that are somatically indistinguishable from the ordinary white-eyed race, yet they are the combined product of several known genes. The purple eye color of *Drosophila* is practically indistinguishable from the eye colors maroon and garnet. In a word we are led again to units in the germ plasm in our final analysis rather than to the appearance of a character.

4. *Inference that Each Character is the Product of Many Genes*

We find that any one organ of the body (such as an eye, leg, wing) may appear under many forms in different mutant races as a result of changes of genes in the germ plasm. It is a fair inference, I think, that the normal units—the allelomorphs of the mutant genes—also affect the same part. By way of illustration I may state that we have found about 50 eye-color factors, 15 body-color factors, and at least 10 factors for length of wing in *Drosophila.*

If then, as I have said, it is a fair inference that the units in the wild fly that behave as Mendelian mates to the mutant genes also affect the organ in question, it follows that many and perhaps a very large number of genes are involved in the production of each organ of the body. It might perhaps not be a very great exaggeration to say that every gene in the germ plasm affects every part of the body, or, in other words, that the whole germ plasm is instrumental in producing each and every part of the body.

Such a statement may seem at first hearing to amount almost to an abandonment of the particulate conception of heredity. But in reality it is only a conclusion based on fact. *The essential point here is that even although each of the organs of the body may be largely dependent on the entire germ plasm for its development, yet this germ plasm is made up of independent pairs of units.*

5. *Evidence that Genes have a Real Basis in the Germ Plasm*

In 1906 Bateson, Saunders and Punnett found that certain pairs of characters in sweet peas did not behave independently of each other, but tended to stay together, or to keep apart, in succeeding generations according to the way they entered the cross. Every year more cases of linkage are found, so that there can be little doubt

that this phenomenon is one of the fundamental attributes of Mendelian inheritance.

While the linkage relations of genes do not *at present* have any immediate bearing on our conception of the nature of genes, they have a very important bearing on the problem of the localization of genes in the germ plasm.

The original evidence that Weismann accepted to show that determiners are carried in the chromosomes, viz., the evidence based on transmission through the protoplasm-free head of the spermatozoon, was made much stronger from Boveri's evidence derived from experimental embryology.

The argument became still more convincing when the facts of sex-linked inheritance and non-disjunction were established. For, it was found that certain characters have the same distribution as do the sex chromosomes, and secondly by the actual cytological demonstration that the rare exceptions to the rule are due to irregularities in the distribution of the sex chromosomes.

All of this evidence has played a rôle in persuading us that the genes postulated for Mendelian inheritance have a real basis and that they are located in the chromosomes. Finally, in *Drosophila,* where there are four pairs of chromosomes, there are also four great groups of linked genes. This coincidence adds one more link to the chain of evidence convincing a few of us that the gene in Mendelian inheritance has a real existence.

CONSIDERATION OF CRITICISMS

I have tried to make clear how the genetic evidence has necessitated the assumption of genes in heredity, and I have pointed out what seem to me to be some of the attributes that it has been desirable to add to the earlier conception of the gene as our knowledge has increased. Now that the ground is cleared, let me try to answer the objections or criticisms which I mentioned at the start, that have been advanced against this kind of hypothesis.

(*A*) *Assumption of Genetic Factors is Arbitrary*

It has been said that by assuming enough genetic factors you can explain anything. This is true; and it is the greatest danger of the factorial procedure. If, for example, whenever one fails to account for a result he introduces another factor to take care of what he can not explain he is not proving anything except that he is ingenious or only naïve. To make good the introduction of another gene in Mendelian work, its presence must be established by the same kind of evidence as that on which the existence of the original factors was established. For example. Bridges found that after eosin eye color had been crossed to a certain red-eyed stock, there appeared in later generations a new class of eye color (Cream II) that was far lighter than eosin. He isolated this new character and showed that the difference between it and eosin was due to a specific gene that in inheritance behaves like other genes, although its action is not apparent on the normal red eye, but is evident on the eye color eosin. Here, then, through experimental tests, the actual demonstration was made that the change in color of the eosin was due to another gene hidden in the normal stock.

(*B*) *Stability of Genes versus Instability of Characters*

It has been objected that it is unreasonable to assume that genes are relatively stable. This objection is based largely on the fact that characters are notoriously fluctuating, and since characters form the basis of our numerical data from which the idea of the gene is derived, it is supposed that genes too must be variable. This is by all odds the most common criticism that has been brought against the idea of genetic factors and the most difficult one to disprove. There are five answers, however, to this objection.

In the first place it has been shown in a number of instances that the variability of the character is due to a mixed or composite population in which there are sev-

eral genotypes present. In other words, it was because most material is itself not uniform that an exaggerated idea arose concerning the nature of the variability of the character.

In the second place, Johannsen's experiments with Princess beans have shown that when the material is homogeneous in successive generations the variability of the character is due to the environment and is not due to changes in the genotype.

In the third place, any pure stock (and especially one that has been made homozygous by inbreeding), so long as it does not vary, is an argument for the stability of the factorial basis. When changes occur in it as they are pretty certain to do, the fact does not in itself prove that the gene under observation has changed, for other genes that affect the character may have mutated. Jennings has recently said[2] that we maintain the constancy of a given gene by assuming that other genes, rather than the original gene itself, have changed. This would be of course on our part a straight evasion of the issue. The criticism would hold if the question involved were a purely philosophical one, as Jennings might unintentionally lead the reader to believe. Fortunately it is becoming more and more possible to demonstrate that changes of this latter kind do take place; for it is possible with suitable material to show in such cases the exact nature of the change. Wherever it has been possible to do this it has been found that a definite mutation in some gene has taken place, or has been introduced into the culture through crossing.

In the fourth place it has been found that more than one mutant gene may be the mate (allelomorph) of the same normal gene. Since no more than two of them may exist at the same time in a given individual, and since linkage experiments have shown in *Drosophila* that these multiple allelomorphs have the same linkage relations to all other genes (*i. e.*, as we interpret the result, each such

[2] *Jour. Washington Acad. Science,* VII, 1917.

set of allelomorphs has the same locus in the same chromosome) this experimental evidence shows that several allelomorphs of the same gene may exist. An interesting relation in regard to these multiple allelomorphs is that they affect chiefly the same part of the body in the same general way. They *may* give a series of types that is discontinuous, such as the quadruple mouse series: yellow, gray white-belly, gray, black; or the more nearly continuous septuple *Drosophila* series: red, blood, cherry, eosin, buff, tinged, white. Whether such a series of characters is large enough to appear continuous or not is a matter of trivial importance in comparison with the established fact that the genes behind such a series arose in the same way as do other mutant genes, and after they have appeared, are as constant as are other genes. There is no experimental evidence to show that the multiple mutant allelomorphs are more likely to arise from each other than they are from the normal allelomorph, and even if this should be true for individual genes it is no more than is true for other "normal" genes, some of which mutate more readily than others. Emerson has shown for corn that one allelomorph of a series is more likely to mutate than others and we have shown for *Drosophila* that certain normal genes, as the one that mutates to produce vermilion eye color, are more likely to mutate than are others.

When Jennings[3] tries to interpret this evidence of continuous series of allelomorphic characters as breaking down all real distinction between mutation and continuous variation, he leaves out of account certain very fundamental considerations. For example, De Vries himself has always urged that mutations may be very small so far as the character change is concerned; the Svalöf evidence shows this in a very striking way, and Johannsen's beans have been for several years a classic case illustrating how minute the characters depending on

[3] *Loc. cit.*

genetic differences may be. It comes, therefore, somewhat as a surprise when Jennings states:

"Certain serious difficulties appear in this view of the matter; I shall mention merely two of them, for their practical results. One is the very existence of the minutely differing strains, which forms one of the main foundations of the genotype theory. How have these arisen? Not by large steps, not by saltations, for the differences between the strains go down to the very limits of detectability. On the saltation theory, Jordan's view that these things were created separate at the beginning seems the only solution."

It should be remembered too that it is possible to make up just as continuous a series of characters with genes belonging to different allelomorphic pairs (even when they lie in different linked groups) as the continuous series from multiple allelomorphs.

If there were any connections between the gradations of character in allelomorphic series and the order in which the characters appear, such a relation might appear to furnish a support to the view that the assumed fluctuation of factors is a sequential process, and that selection actually helps forward the direction in which mutation is likely to take place, a view that Castle has at times apparently espoused. As a matter of fact, there is no such relation known—the *known* facts are exactly to the contrary; for the actual evidence from multiple allelomorphs shows that genes may mutate in all directions and also that extreme mutations such as white eyes arise suddenly from red and not by graded steps

In the fifth place, the most recent work on *Drosophila* has shown not only that every gene may act (and often does act) as a differential for characters conditioned by other genes, but also that there are genes whose most visible effect is only on certain characters which may therefore be said to be modified by the former. It would be a great mistake to suppose that these modifying genes are unique in any essential respect—the kinds of effects

that they produce grade off into effects that the ordinary genes produce. The chief interest in demonstrating (instead of speculating about) such genes is that they go far towards helping us to a clearer interpretation of certain evidence that was heretofore obscure or misinterpreted. Wherever the history of the origin of these genes is known it has been found to be the same as for other genes and their behavior in Mendelian inheritance is precisely the same. Nevertheless, Jennings has, in the paper already referred to, left certain implications in regard to them that, if not clearly understood, may throw the subject into worse confusion than before. He seems to imply —perhaps he does not really intend to do more—that since through such modifying genes a perfectly continuous series of modifications of a character may exist, all real distinction becomes lost between continuous and discontinuous variation. Now as a matter of fact perfectly continuous characters, if due to overlapping of the separate modifications, can be statistically handled, as Johannsen has done for beans and as Jennings himself has done for size differences in paramecium. Other ways are also known by which the localization in the chromosomes of modifying factors can be studied by methods that no student of Mendelian heredity can afford to reject.[4] All of this is familiar, of course, to Jennings. He means, however, to suggest that if the work on *Drosophila* continues for another fifty years, so many modifiers *may* be found that the characters will form a continuous series. But suppose the mutants do become so numerous that it is impossible to distinguish between any two by inspection. Are we then to reject all the body of evidence that is fast accumulating that the modifying genes are ordinary Mendelian factors? It would be the height of absurdity to throw overboard all this experimentally determined evidence as to the actual method of origin and inheritance of these genes because a time may come when members of a series have become so numerous that we

[4] See "Mechanism of Mendelian Heredity," pp. 192–4.

will be too much bored to make the tests that will distinguish a given new member from some one or other of the old ones. But Jennings may reply, suppose the selectionist claims that his material is already in this finely triturated condition! If, so, the answer is that by suitable selection experiments an analysis may in many situations still be made, and, secondly, the evidence, even from Castle's rats, is far from establishing that he is dealing with such a sublimated process. On the contrary, there is much in them to indicate that they may be capable of being handled by rather simple Mendelian methods, as MacDowell has shown.

As a matter of fact, when indistinguishable characters are the product of one or another *modifier,* the identification of the two genes involved, as independent, is perfectly easy and certain by means of linkage relations. If a particular material is not sufficiently worked out to make this test possible, is that a sufficient reason why we should refuse to accept evidence where it can be obtained? And if there are indistinguishable characters that are the product of one or of another *allelomorph,* of course it can not be determined which allelomorph produces the result; but as, ex hypothesi, each allelomorph produces the same indistinguishable result, a discussion of such a question would be as profitable as the ancient one of the number of angels that can stand on the point of a needle.

In conclusion then it may be said that by stable or constant genes we do not necessarily mean that the gene is absolute in the sense that a molecule is absolute, for we can not know this at present. We might mean by stable genes that even if there is a variability of the gene the variation takes place about a mode; and if in a given individual the extreme of variation was caused by a corresponding extreme in the variation of the gene, still the experimental evidence shows that in the many cell-generations through which that individual's germ cells pass to produce the sperms or the eggs, the genic variation, if there is any, is still about the *original* mode and that no

new mode has been established unless a mutation has occurred. This latter interpretation is indeed in contradiction to the idea that the gene is a single molecule, for molecules are not supposed to vary about a mode. At present either interpretation is compatible with the evidence, which does not discriminate between them.

(*C*) *Non-Contamination of Genes*

At the time when Darwin wrote and for many years afterward it was supposed that any new or unusual trait of character would become obliterated by repeated crossing with the normal or average individual of the species. This was perhaps the most serious difficulty that Darwin's theory of natural selection met with. It will be recalled that in order to overcome it Darwin made a concession that in principle amounted to an abandonment of the origin of characters through natural selection of chance variations. He admitted that only when a new character appeared in a large number of individuals at the same time was there an opportunity for its perpetuation.

In sharp contrast to this earlier view, all the evidence from Mendelian heredity goes to show that however often a new character, that rests on a genetic change in the germ plasm, may have been kept out of sight by crossing to dominant individuals, whenever the character emerges from the cross, it shows at once that its gene has not been contaminated by contact with other genes. This conclusion is an enormous gain for the theory of natural selection based on chance variation, and at the same time is an equally strong argument to show that genes remain stable, and are not infected or mixed in the presence of other contrasting genes.[5] Let me illustrate by a case of my own.

[5] Those who in their haste try to show that Darwin must have meant by fluctuating variation small mutations, since he assumed such fluctuations to be inherited, might well ponder the difference between the two kinds of variation cited above. If Darwin had realized the difference referred to, he would not have had to make the damaging concession forced upon him by his critic, a professor of engineering, Fleeming Jenkin, in the *North British Review* (June, 1867).

There is a mutant called "notch" (Fig. 1) characterized by a serration at the ends of the wings. The factor that causes this is sex-linked, dominant in regard to the

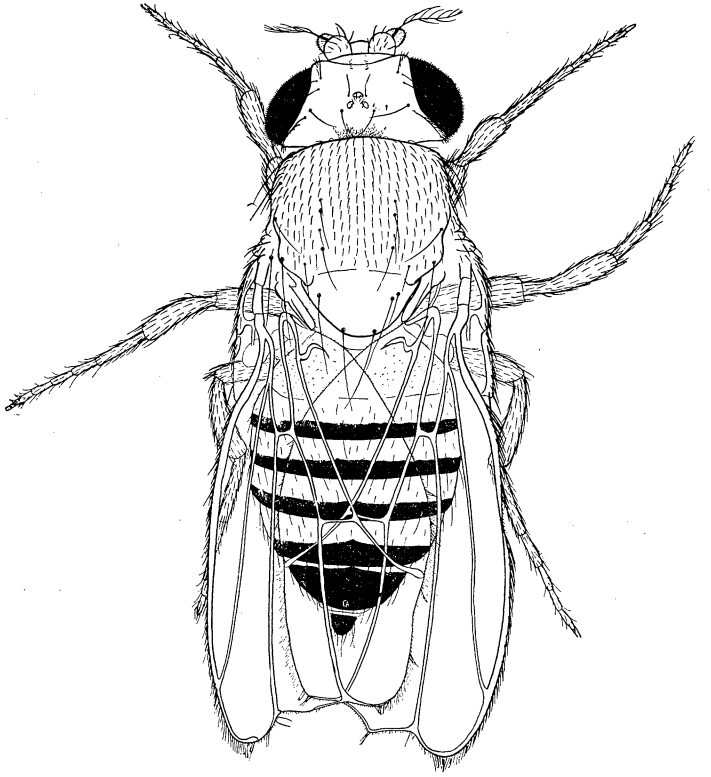

FIG. 1. Notch female.

wing character but recessive in its lethal effect. A female with notch wings carries the gene in one of her X-chromosomes and the normal allelomorph in the other X-chromosome. Half of her sons get the former and die, the other half get the latter X-chromosome and live. As there are no lethal bearing males, the females must in every generation be bred to normal males. For twenty generations such matings have been made. Each time there have come together in the same female one X-chromosome carrying the gene for notch and its mate carrying the normal allelomorph. Selection of those females that

showed the least amount of notch, changed, after a few generations, the outward character of the notch stock so that at least half of those females that carry the notch gene came to have normal wings. It might have seemed that the gene itself had changed, possibly through contamination with the normal gene, were such a thing possible. On the contrary, if these females with normal wings are outcrossed to a male of any other stock, all the daughters that carry the notch gene have the notch in the original (atavistic) condition, showing that the gene still acts in all its original strength. Moreover, suitable experiments have shown that as a result of selection, a modifying gene, already present in the original stock, has been isolated. This gene modifies notch (although it produces no visible effect on the normal wing) in such a way that the notch is less likely to appear. The evidence furnishes the twofold demonstration that the gene for notch has not changed through contamination, and that there is present a new and definite gene that does account for the change.

(*D*) *Methods of Inheritance that are not Mendelian*

It has been claimed that Mendelian inheritance is only one kind of inheritance and applies to only a limited group of characters. It has even been implied that the kind of characters involved in the process of evolution can not be inherited in this way because, it is affirmed, evolutionary characters are not like Mendelian characters. It is known that certain plastids, such as chloroplasts, that lie in the protoplasm are transmitted as a rule only through the egg protoplasm. There can be no doubt that this sort of transmission takes place. In principle it is not different from the transmission of certain kinds of bacterial diseases like that of pebrine in the egg of the silkworm moth. Any inclusion in the cytoplasm capable of increasing there by division would be mechanically carried to all the new cells arising by division and there-

fore into the egg cell also. Should the sperm cell strip itself free of most of that part of the cytoplasm that contained these inclusions, the spermatozoa alone of all the cells in the body would be free from these cytoplasmic materials, and in consequence would not transmit them.

So long as we recognize with what we are dealing here it is largely a matter of personal choice whether we prefer to include plastid transmission through the egg (or even through the cytoplasm of the sperm in special cases) under the term heredity.

The number of cases in which plastid inheritance is known to occur is very limited,[6] while Mendelian heredity includes the vast majority of characters about whose inheritance we know something definite.

But it is a far cry from these cases of transmission of plastids to the view that the cytoplasm transmits equally with the chromosomes; or that the cytoplasm transmits the fundamental attributes of the organism and that the chromosomes transmit only the more superficial characteristics—a view that Boveri discussed in detail in 1903, and which was a favorite topic of his on several later occasions. He changed entirely as the evidence came in and finally abandoned the view in his last paper (1914).

This is an old and familiar topic with embryologists, but since it has been recently revived, a brief statement in regard to it may not be out of place. Fortunately this view is no longer a matter of opinion but of experimentally determined evidence.

In 1912, Toyama described some cases in silkworm moths of what is known as maternal inheritance—cases in which certain characteristics that develop in the hybrid embryo are like those of the maternal stock. He found cases involving the color of the yolk, shape of the egg, and the pigment (not present as such in the egg) that develops after the serosa is formed. By breeding tests it

[6] If chondriosomes are "formative" materials as certain writers claim, the type of plastid inheritance may include a larger group of characters than we suppose at present.

was made clear that the cytoplasm transmits these characteristics only because they have been impressed on the cytoplasm by the chromosomes at some earlier stage in the history of the egg cell. They are strictly Mendelian (Fig. 2).

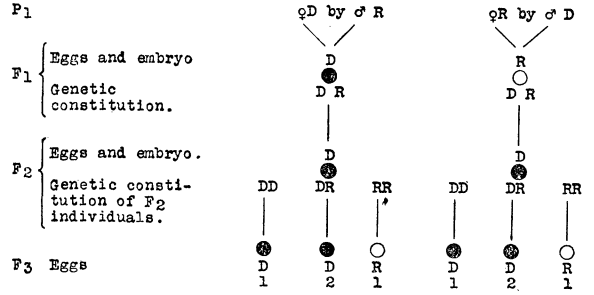

FIG. 2. Maternal inheritance in the silk-worm moth according to Toyama.

It has also been suggested that the chromosomal, Mendelian genes affect only trivial characters such as color, while the more *fundamental* characters are carried in the cytoplasm.[7] There are in reality no grounds for assuming that some characters are more fundamental than others; or that such hypothecated fundamental characters have a different mode of inheritance. The old-fashioned distinction between ordinal, class, family and generic characters has long been recognized as entirely artificial and conventional while the so-called promorphological characteristics such as shape of egg, type of cleavage, axial relations are as variable as are other characteristics, and some of them, such as shape of egg, location of micropyle, etc., have been shown to fall under the Mendelian formula. Take, for example, the following list of characters and try to decide whether they are fundamental (generic) or only trivial; they are all Mendelian in some cases at least:

Sterility, several types of which are recognized as Mendelian;

[7] Boveri, 1903; Loeb, 1916.

Sex, the inheritance of which is shown in many cases to be associated with sex chromosomes;
"Apterous," loss of wings in certain stocks of *Drosophila;*
"Eyeless," partial or complete loss of eyes;
"Extra legs," duplication of part or of entire legs which in one race shows Mendelian sex-linked transmission;
Heliotropism, loss of positive response to light in one stock of *Drosophila.*

Until there is forthcoming some direct evidence that the cytoplasm apart from its contained plastids transmits more fundamental characteristics than the chromosomes, the claim that such a difference exists is not only entirely speculative, but has been shown not to be true for a number of characters. No doubt the idea arose from the fact that when the egg begins to develop it is the protoplasm that exhibits most of the phenomena concerned with the early development of the axial and bilateral relations, the type of cleavage and the formation of the organs of the embryo. But this kind of evidence shows no more than that these characteristics are then present in the cytoplasm; it does not show whether they have come from the chromosomes in the early history of the egg cell, or were, as assumed, inherent properties of the cytoplasm as such. In recent years, however, it has been possible in a few cases, like those of Toyama, to get experimental evidence bearing on this point and it has shown beyond dispute that such cytoplasmic types of behavior are impressed on the cytoplasm by the chromatin in the same way presumably as are all Mendelian characteristics.

No one has denied, so far as I know, that the cytoplasm is essential for development. That it is transmitted largely, if not entirely, through the cytoplasm of the egg is too well recognized to debate, and that it may contain substances that have never been a constituent part of the nucleus and which may form the basis through which material of nuclear origin may act must be freely granted

as an important theoretical possibility. But it must not be forgotten that the only characters that we know anything about in genetics are under nuclear control with the exception of plastids that can themselves multiply in the cytoplasm.

There is a special case of inheritance that has been called cytoplasmic that may equally well have a chromosomal explanation. Goldschmidt finds that he can account for certain of his results in gypsy moths by ascribing certain values to the cytoplasm. Thus he says the two factors for femaleness (FF) are transmitted from the mother to her daughters and the latter transmits again to their daughters, etc. In other words, the factors are carried only in the egg-producing line. Goldschmidt concludes that the evidence proves that the "FF complex is inherited . . . in the protoplasm of the female." Now in moths in which the female is the heterogametic sex, the Y chromosome (or the W chromosome to use a different nomenclature) is transmitted only by the female line and should this chromosome carry the factors in question all the requirements of the experiment would be fulfilled. There is no way of determining from this evidence alone whether the case belongs to the plastid type of inheritance, or is a case of W inheritance, except by finding species in which the female normally lacks the W sex chromosome, or by some anomalous condition has lost it as in the 55 chromosome females that Doncaster has found in the moth *Abraxas*.

There is still another rôle that the cytoplasm may play in determining the nature of the next event to occur. In Phylloxerans it has been shown that a whole sex chromosome is eliminated from the small eggs and in consequence a male results from them. The presumption here is that the effect is through the cytoplasm determining the distribution of the chromosomes, but it must be conceded that the same environmental changes that affected the cytoplasm may have had a simultaneous effect on one of the sex chromosomes. In the case of certain generic

crosses in pigeons, Riddle, confirming Whitman's discovery, finds that when an enforced series of eggs are laid, their chemical composition is changed and that they produce at certain times a preponderance of males. Since the female here is the heterozygotic sex (ZW) the results are such as would follow a direct influence on the sex chromosomes when the polar body is eliminated. Information concerning sex-linked inheritance in these forced offspring should settle the question.

To sum up, it may be said that "plastid" inheritance is at present the only known method of transmission of factors that does not come under Mendel's laws. The three principal kinds of Mendelian inheritance known at present fall into the following groups:

1. Autosomal inheritance, where transmission is equally to both sexes, or to all individuals of hermaphroditic species.
2. Sex-linked inheritance, (*a*) where the distribution of characters coincides with the distribution of the X chromosomes in the *Drosophila* type, and of the Z chromosomes in the *Abraxas* type; and (*b*) where the distribution of characters coincides with the distribution of the Y chromosome (as illustrated by the fertility of the male of *Drosophila* that depends on the presence of the Y chromosome) or of the W chromosome in moths.
3. Inheritance due to unusual distributions of chromosomes, as seen (*a*) in doubling of their number (tetraploidy); (*b*) in non-disjunction, as in the 15-chromosome type of *Œnothera* and the XXY type of female in *Drosophila;* (*c*) in irregularities of synapsis as seen in species hybrids such as *Pygæra.* This group (3) is at present only provisional and will no doubt be broken up at some future time into its different parts.

The case of maternal inheritance, spoken of above (other than Y or W linked or plastid inheritance), has been

shown to be only deferred Mendelian inheritance traceable to the chromatin of the nucleus in which the characters shown by the egg or the embryo have already been determined before fertilization by the chromatin of the mother alone. In consequence the appearance of the Mendelian ratio is deferred to a succeeding generation (F_3).

(*E*) *Action of Genes during Embryonic Development versus their Distribution in Heredity*

On several occasions I have urged the importance of keeping apart, *for the present at least,* the questions connected with the distribution of the genes in succeeding generations from questions connected with the physiological action of the genetic factors during development, because the embryological data have too often been confused in premature attempts to interpret the genetic data. It has been urged that such a procedure limits the legitimate field of heredity to a process no more intellectual than that of a game of cards, for Mendelism becomes nothing but shuffling and dealing out new hands to each successive generation. My plea is, I fear, based largely on expediency, which may only too easily be interpreted as narrow-mindedness; yet I hope to be amongst the first to welcome any real contribution concerning the nature of genes based on the chemical changes that take place in the embryo where the products of the genes show their effects. In fact I do not know of any other more direct way in which we can ultimately hope to find out the nature of the materials that we think of as genes in the germ cells.

But experience has shown, I think, that only too often the embryological data have been used to interpret the transmission data to the detriment of both subjects; I regret to see the inevitable difficulties that are natural, at present, to the field of embryology thrust upon the other subject, where the problem is comparatively simple; and

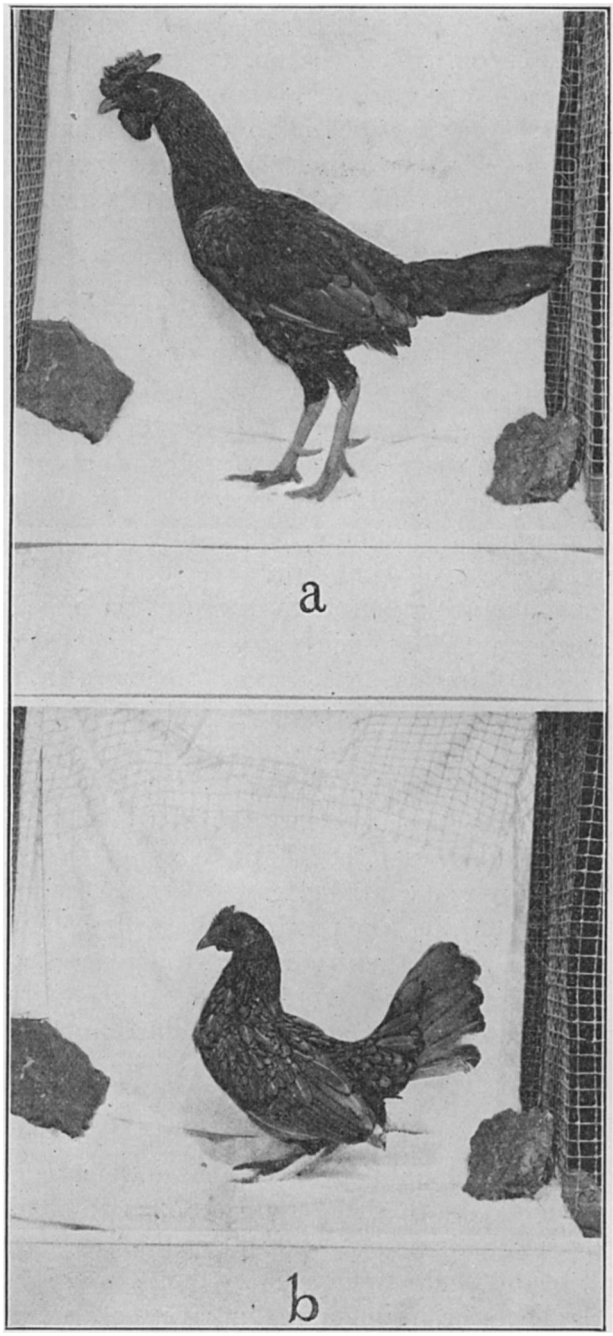

FIG. 3. Male, *a*, and female, *b*, Sebright.

so far as it has progressed, understood. Do not understand me to say that I think all the problems of heredity have been solved, even with the acceptance of the chromosomal mechanism as the agent of transmission.[8] In fact, I think that we are only at the beginning even of this study, for the important work of McClung, Wenrich, Miss Carothers and Robertson shows that there are probably

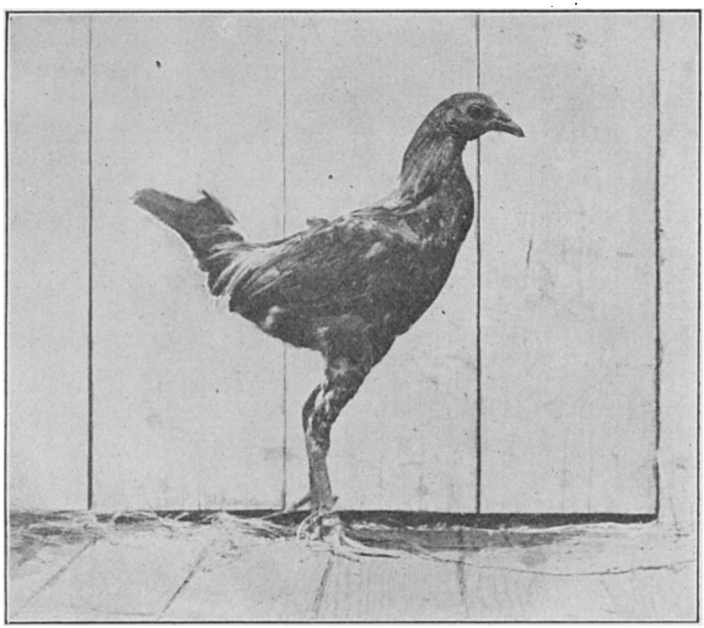

FIG. 4. Male, black-breasted game-bantam.

many surprises in store for us concerning *modes of distribution* of Mendelian factors. Moreover, the method by which crossing over of allelomorphic factors takes place is still in the speculative stage, so far as the cytological evidence is concerned, as are also many questions as to how the lineally arranged factors hold their order during the resting stages of the nucleus and during the condensed stages in the dividing chromosomes.

[8] The statement that I made in my recent book on the "Critique of the Theory of Evolution," that the *traditional* problem of heredity has been solved, is not in contradiction with the above statement which concerns the future problems of heredity.

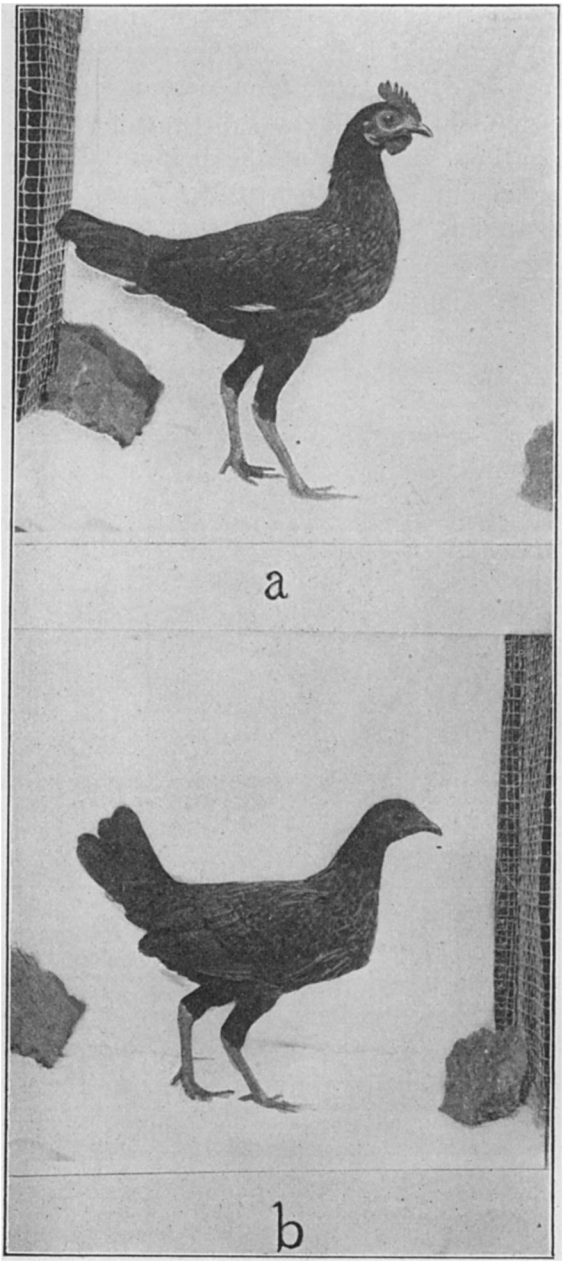

FIG. 5. F_1 male, *a*, and female, *b*, out of Sebright by Game.

It does not seem to me to lessen in any way the importance of embryology to keep its problems for the present separated from those of the method of transmission of hereditary characters. It may well be that there are more important discoveries to be made in future in the field of embryology than in genetics, and that when the subject of chemical embryology has arrived at its goal it may be worth while to combine the two subjects into a single one. I am also aware that to many persons the interest in genetics is greatly increased when certain stages can be demonstrated through which the genes bring about their results. Far from being in opposition to such interests, I can illustrate this very point by a case of my own. The cock bird of the Sebright bantam is "hen-feathered" (Fig. 3*a*), *i. e.,* certain of the secondary sexual characters are like those of the hen (Fig. 3*b*). This is most noticeable in the short neck, back and saddle feathers as well as in the absence of the long tail feathers. When these birds are crossed to game bantams (a race in which the male has the usual secondary sexual characters, Fig. 4), the F_1 cocks are hen-feathered (Fig. 5*a*). This is true both when Sebright ♂ is crossed to game ♀ and when game ♂ is crossed to Sebright ♀. The latter cross shows that the dominant character is carried by the female Sebright as well as by the male.

When these F_1 birds are inbred, they produce in the next generation (F_2) both cock-feathered and hen-feathered males. There is complete segregation of the types that went into the cross. Whether one or two genes for hen-feathering are present is not entirely certain, but that Mendelian segregation occurs there can be no doubt.

I was led to see what would happen when the hen-feathered birds were castrated. Goodale had shown that when the hen of normal breeds is spayed, she develops the full male plumage, including the special feather regions in which the Sebright is hen-feathered. At the time of castration, a few feathers were removed. The new ones that came in showed at once that a great change

had taken place both in the size, shape and color of the new feathers (Fig. 6), which became like those of the "normal" male. Since the F_1 birds were heterozygous,

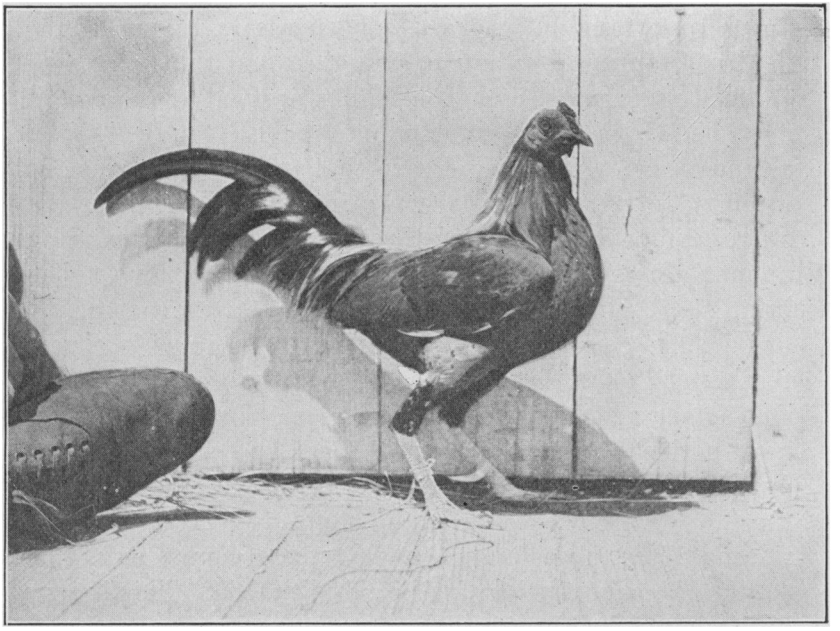

FIG. 6. Castrated F_1 male, originally like male in Fig. 5, *a*.

and the F_2 birds used might also have been heterozygous, it became important to castrate the Sebright males. This has been done and the same complete change takes place in them, as the accompanying figures of the birds (Fig. 7) and of a few of their feathers (Figs. 8 and 9) show very clearly.

Goodale's evidence from the spayed hen makes probable the view that the ovary of the hen produces some internal secretion that inhibits in her the full development of her plumage which is potentially the same as that of her male. After removal of the ovary the inhibition is removed and when the hen moults she develops her full possibilities of plumage. Similarly in the hen-feathered male, some internal secretion must inhibit the development of certain of the secondary sexual characters.

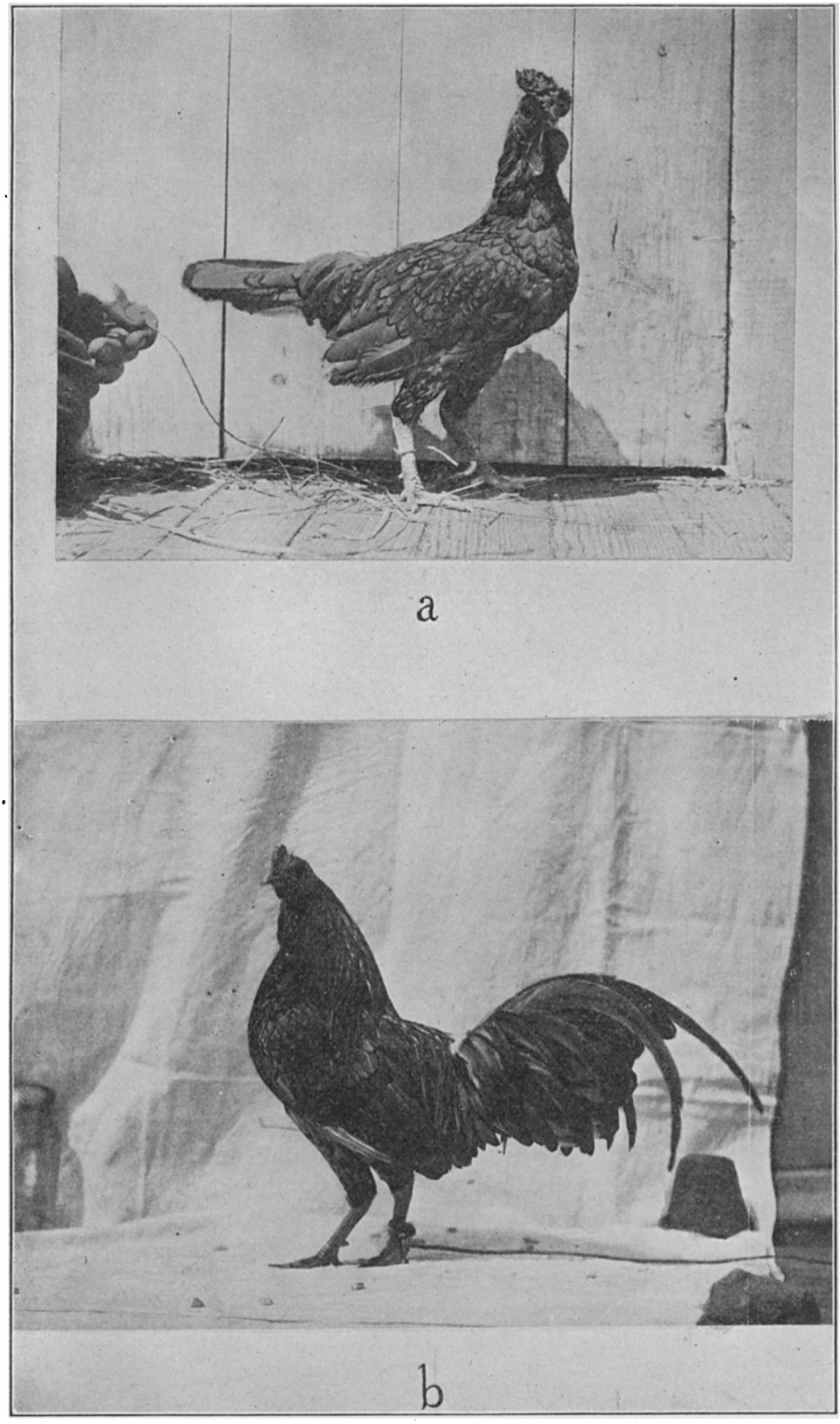

FIG. 7. Sebright male, *a*, and similar bird after castration, *b*.

Here then we get an idea of one of the stages through which the products of Mendelian genes for hen-feathering produce their results. The presence of these genes within

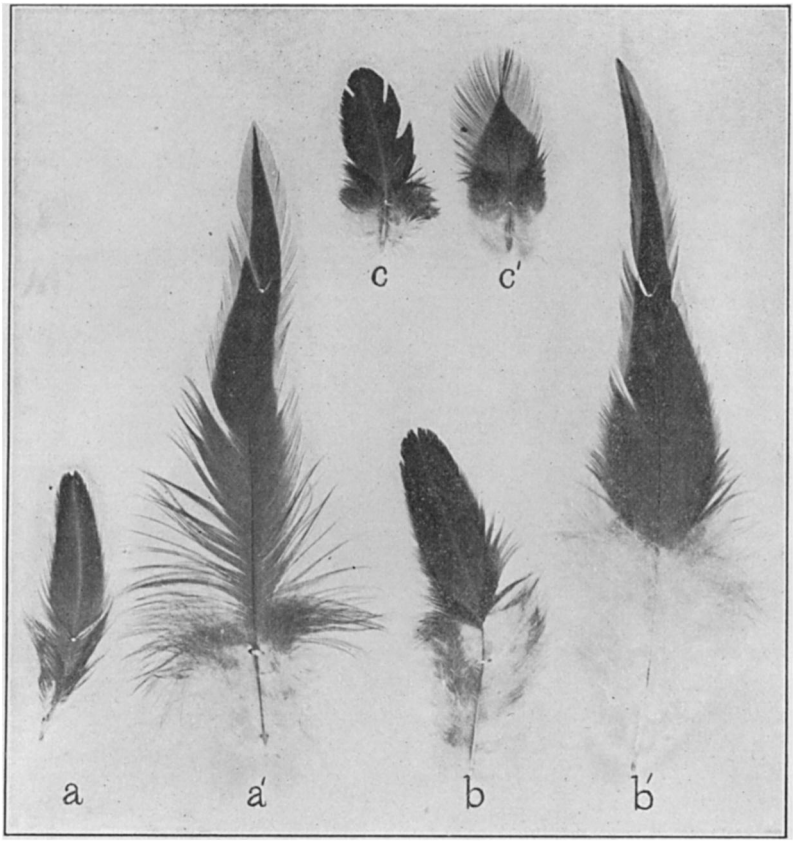

FIG. 8. Feathers from F_1 cock (like that in Fig. 5*a*) before *a*, *b*, *c* and after *a'*, *b'*, *c'* castration; *a*, *a'* hackle, *b*, *b'* saddle, *c*, *c'* wing.

the male birds causes the testes to produce some substance that carried into the body inhibits the full development there of certain feathers. The presence of these genes in the other cells of the body is without influence on the plumage, except in the presence of the testes. The activity of the latter is such that a substance is produced there that has an inhibitory effect.

In other words, we are fortunate enough in this case

to be able to show a particular stage in the chain of events by which the character of certain feathers is influenced. I need not point out that there is not the slightest reason to identify the substance produced in the testes with the

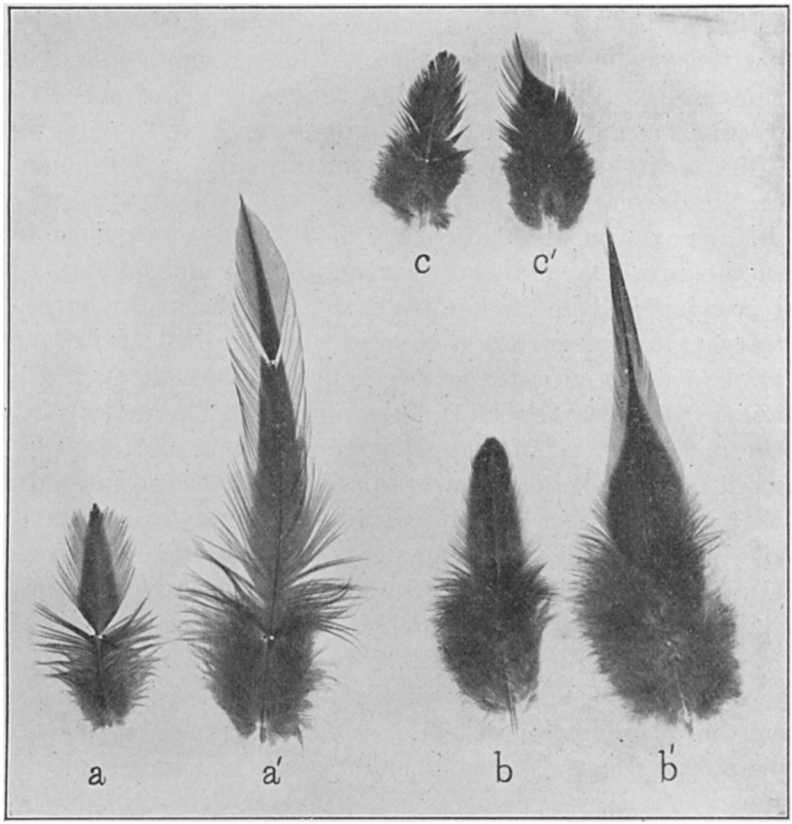

FIG. 9. Feathers from Sebright cock (like Fig. 3*a* or Fig. 7*a*) before *a*, *b*, *c* and after *a′*, *b′*, *c′* castration; *a*, *a′* hackle, *b*, *b′* saddle, and *c*, *c′* wing.

substance of the gene; the chemical composition of the internal secretion may be entirely different from that of the gene, the latter producing its result in conjunction with substances resulting from other genes. There is every reason for supposing that the way in which the effects are produced here are the same as in all development when the end result is the collective product of substances pro-

duced by the hereditary genes—a single gene difference turning the scale in this way or in that. In this case we have, I think, an excellent illustration of the difference between the mechanism of inheritance and the chemical effects of genetic factors on development. Highly interesting and important as it undoubtedly would be to work out these connections, yet the evidence is very explicit in showing that the distribution of the materials of heredity during the maturation process of the egg and sperm is different in kind from their action through the cytoplasm on the developing organism.

For purposes, then, of closer analysis, it seems desirable in the present condition of genetics and embryology to recognize that the mechanism of distribution of the hereditary units or genes is a process of an entirely different kind from the effects that the genes produce through the agency of the cytoplasm of the embryo. The activity of the cytoplasm is, of course, bound up with the environment in which it takes place—a relation that is so intimate that in most cases the constitution of the cytoplasm and the nature of the environment in which it finds itself are studied as two sides of the same problem. It is true that the mechanism of Mendelian heredity may also be affected by the environment, certainly by the external environment, as Plough has shown for heat; and also probably by the cytoplasmic environment since Bridges has shown that the process is somewhat different in young and old flies. But there is no evidence that the relation of the maturation process to the environment is in any way related to the reactions that go on between the cytoplasm of the developing embryo and its environment, and it has only led to confusion whenever an attempt has been made to deduce from the nature of the embryonic reaction the nature of the mechanism that distributes the genes in heredity.